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Genes, Synapses, and Long-Term Memory

ERIC R. KANDEL*
Howard Hughes Medical Institute and Center for Neurobiology and Behavior, College o Physicians and Surgeons of Columbia University, New York, New York

Cognitive psychological studies have shown that there are at least two distinct types of learning: learning about people, places, and things (explicit or declarative forms of learning) and learning motor skills and perceptual strategies (implicit or procedural forms of learning). These two forms of learning have been localized to different neural systems within the brain. Explicit learning requires regions within the temporal lobe of the cerebral cortex including the hippocampus, whereas implicit learning involves the specific sensory and motor systems recruited for the particular task [for review, see (1)]. As a result, implicit learning has been studied in a variety of simple reflex systems, including those of invertebrates such as *Aplysia, Hermissenda,* and *Drosophila.* By contrast, explicit forms of learning can best (and perhaps only) be studied in mammals.

In this brief review I will consider the question: To what degree do these two major learning processes share common molecular steps?

One clue to shared mechanisms comes from the study of memory storage, the retention of information acquired through learning. Memory has stages and is commonly divided into two temporally distinct phases: short-term memory, which lasts minutes or hours, and long-term memory, which can last days, weeks, or even longer. Studies of both implicit and explicit learning indicate that a transient application during learning of inhibitors of mRNA and protein synthesis selectively block the induction of long-term memory without affecting short-term memory. By contrast, a similar application of inhibitor has no effect on the maintenance of long-term memory once it is established. These studies suggest that the switch to long-term memory requires the induction of genes and proteins not required for the short-term memory.

I will describe recent studies that have begun to identify some of the proteins involved in the switch from short- to long-term memory. Studies of sensitization of the gill- and siphon-withdrawal reflex in *Aplysia,* a simple form of implicit learning, have revealed a representation of short- and long-term memory at the cellular level. Training leads to a strengthening of the connections between the sensory and motor neurons of this reflex. The short-term enhancement of synaptic strength occurs by means of posttranslational modification of preexisting proteins mediated primarily by the presynaptic action of cAMP-dependent protein kinase (protein kinase A) but also involving protein kinase C, which results in an increase in transmitter release from the presynaptic terminals of the sensory neurons. The long-term process requires cAMP-mediated gene expression and new protein synthesis, which results in the growth of new synaptic connections Studies by Yin et al. (2,3) have shown a similar dependence of long-term memory in *Drosophila* on cAMP-mediated gene expression.

Is there a similar representation of memory storage for explicit forms of learning in the mammalian brain? Memory storage for explicit forms of learning require structures within the temporal lobe including the hippocampus. The hippocampus itself has 3 major (and a number of minor) synaptic relays in series. Input to the hippocampus comes from the neurons of the entorhinal cortex by means of their axons, the perforant pathway, that synapse on the granule cells of the dentate gyrus. The granule cells in turn send their axons, the mossy fiber pathway, to synapse on the pyramidal cells of the CA3 region. Finally, the axons of the pyramidal cells in the CA3 regions, the Schaffer collateral pathway, terminate on the pyramidal cells of the CA1 region. Each of these pathways makes a direct monosynaptic connection on its target cells, and damage to a single pathway within the hippocampus is sufficient to produce memory disturbance in humans.

In 1973, neurons of the hippocampus were shown to have plastic capabilities of the kind that might be required for memory storage. Brief, high-frequenc trains of action potentials in any one of these 3 neural pathways within the hippocampus produce an increase in synaptic strength in that pathway. The increase can last for hours in the anesthetized animal and for days and even weeks in the freely-moving animal. This activity-dependent increase in synaptic strength is called long-term potentiation (LTP).

These three pathways can be studied ex vivo in hippocampal slices, where all 3 pathways have been shown to use glutamate as their transmitter, and in all three pathways LTP looks quite similar. Nevertheless, the pathways use two different inductive mechanisms for triggering LTP, distinguishable by both the critical roles of different glutamate receptors in initiating LT and the pre- or postsynaptic locus of induction. In the medial perforant and the Schaffer collateral pathways, LTP is initiated in the postsynaptic cell. Induction in-

*Correspondence to: Eric R. Kandel, Howard Hughes Medical Institute and Center for Neurobiology and Behavior, College of Physicians and Surgeons of Columbia University, 722 West 168th Street, New York, NY 10032.

volves activation of the NMDA-type glutamate receptor and requires influx of Ca^{2+} into the postsynaptic cell through the NMDA receptor channel. By contrast, LTP in the mossy fiber pathway is induced presynaptically and requires neither activation of the NMDA receptor nor Ca^{2+} influx into the postsynaptic cell.

LTP has been studied extensively at the NMDA-dependent synapses and particularly in the synapses of the Schaffer collateral pathway. Here, the Ca^{2+} influx triggered by activation of the NMDA receptor recruits several second-messenger kinases in the postsynaptic cell, including calcium/calmodulin kinase II, protein kinase C, and tyrosine kinases. Once induced, LTP in the Schaffer collateral pathway shows distinct phases. There is an early phase, lasting 1–3 hr, that does not require protein synthesis and a later persistent phase that requires the activity of protein kinase A as well as new protein and RNA synthesis.

Is the requirement for cAMP-mediated protein and RNA synthesis a general feature of LTP in the hippocampus? Does NMDA receptor-independent LTP in the mossy fiber pathway also have this requirement? In the mossy fiber system, LTP has both an early and a late phase, and protein kinase A contributes to both phases. We have found that the early phase is induced presynaptically and involves a mechanism that is protein synthesis independent, whereas the late phase, whose locus of expression is as yet undetermined, requires protein and mRNA synthesis.

Thus, the early phase of LTP in the mossy fiber synapse, which involves protein kinase A, is distinct mechanistically from the early phase of LTP at the Schaffer collateral synapses, which depends instead on the Ca^{2+}/calmodulin kinase, protein kinase C, and tyrosine kinases. The mechanisms for the early phase of LTP in the two pathways are distinguished not only by the kinases recruited for their expression but also by the locus of induction. Schaffer collateral LTP is induced postsynaptically and requires activation of the NMDA receptor channel and the subsequent influx of Ca^{2+}. By contrast, LTP in the mossy fiber system is induced presynaptically and does not require activation of NMDA receptors or Ca^{2+} influx into the postsynaptic cell.

Despite these differences in induction and expression of the early phase, the mechanisms for the late phase of LTP in these 2 synaptic pathways seem similar in outline, although they are likely to differ in detail. In both pathways, the late phase is dependent on new RNA and new protein synthesis, and in both cases, the cAMP-dependent kinase seems to be involved. In turn, these mechanisms for the late phase of LTP, thought to be important for long-term memory storage following explicit forms of learning, resemble those utilized in *Aplysia* and in *Drosophila* for storing behavioral long-term memory for implicit tasks. This convergence of findings suggests that even though implicit and explicit forms of learning are fundamentally different, they do not necessarily use different mechanisms for storing long-term memory. Rather, the two different classes of learning can, at least in certain cases, use a common class of molecular mechanism for converting a labile short-term form into a stable long-term form: the induction of genes by cAMP and protein kinase A. As a corollary, these several findings suggest that, even though different forms of learning recruit activity in a variety of parallel and distributed neuronal pathways (each of which is likely to have a number of synaptic relays capable of giving rise to distinctive short-term processes), the molecular mechanisms utilized at these various sites for the storage of long-term memory may be quite restricted and conserved.

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